REMARKS

Claims 1-26 are currently pending.

Sworn English language translations of Applicants' foreign priority documents, JP 2002-250991 and JP 2002-250992 are also being filed concurrently herewith.

I. The Rejections Under 35 USC§112

Claims 1-7 are rejected under 35 U.S.C. §112 as allegedly being indefinite.

The Examiner states that the entire claim is poorly worded and so unclear that the claim must be corrected. The Examiner also states that the claims are generally narrative and indefinite, failing to conform with current U.S. practice and that they appear to be a literal translation into English from a foreign document and are replete with grammatical and idiomatic errors.

The Examiner states the phrase "an activity of inhibiting the onset of alcoholic hepatopathy and an activity of healing it" is unclear and suggests rewording.

The Examiner states the phrase "the composition comprising an unadsorbed fraction which is formed by subjecting a barley shochu stillage byproduced in the production of shochu from a barley as a raw material to solid-liquid separation to obtain a liquid fraction and subjecting the liquid fraction to a separation treatment by adsorption using a synthetic adsorbent" is unclear.

The Examiner states the phrase "unadsorbed fraction" is uncertain.

The Examiner questions the unit of measurement in the phrase "plural peptides having an average chain length of from 3.0 to 5.0."

The Examiner also requests the claims recite the genus-species name of "barley" in parentheses after the term "barley".

Applicants respectfully submit that the present claims are clear and definite as written and that they particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, second paragraph, in view of the following remarks.

First of all, Applicants respectfully traverses the Examiner's statements that the claims as originally filed are poorly worded and replete with grammatical and idiomatic errors. However, to facilitate prosecution, the claims have been amended for clarity. As to the activity of inhibiting, claim 1 as amended recites "wherein said compound is capable of inhibiting the onset of alcoholic hepatopathy and/or capable of healing alcoholic hepatopathy." The phrase "unabsorbed fraction" has been clarified to indicate that "unabsorbed product of said separation treatment is said unabsorbed fraction." The amounts of amino acids in the peptides are "% by weight."

As to the unit of measurement for the phrase "plural peptides having an average chain length of from 3.0 to 5.0," Applicants' specification page 64 indicates that the average chain length of the peptides by a TNBS (2,4,6-trinitrobenzenesulfonic acid) method. Said method is

well known in the art. See, for example, the official Website of Kiku-Masamune Sake Brewing Co., Ltd. (http://www.kikumasamune.co.jp/tec_repo/).

The following description is found at "Section 3: Relations of types of rice-malt-yeast cultures (*syubo*) to peptide content of refined sake; supplementary note; summary of sections (pdf 48k)" under "First article: What influence does pure-culturing *(kimoto-zukuri)*) have on the quality of sake? (The peptide content of sake tends to increase in the process of pure-culturing.)", which is posted on the above-identified homepage.

Average (Mean) chain length of peptides = (a - b)/(c - b)

where *a* denotes concentration (mM) of amino acid after acid hydrolysis; *b* denotes concentration (mM) of amino acid before acid hydrolysis (i.e. free amino acid); and *c* denotes concentration (mM) of amino groups of an N-termini measured by the TNBS method.

The TNBS method is a method for measuring the concentration of the amino group of an N-termini.

More detailed information is also found in Silvestre et al, Analysis of Protein Hydrolysates. 1. Use of Poly(2-hydroxyethylaspartamide)-Silica Column in Size Exclusion Chromatography for the Fractionation of Casein Hydrolysates, *Agric. Food Chem.*, 42, 2778-82 (1994) (copy attached).

With regard to the Examiner's statements concerning the claim term "barley," Applicants respectfully submit that the term "barley" is well known in the art.

The following is submitted for the understanding of the Examiner. First of all, usually, two-rowed barley is used for production of distilled spirit (*shochu*). In general, various kinds of barley are classified into the following categories.

Six-rowed barley --- Hulled barley (small barley), Naked barley

Two-rowed barley --- Malting barley, Food barley (large barley)

Other than the above classification, they are alternatively classified into glutinous barley and non-glutinous barley.

Historically, two-rowed barley was introduced from Europe as a raw material for beer in the early Meiji era, which marked the start of two-rowed barley cultivation in Japan. Because of various requirements to be qualified as a beer material, including a large grain size, the high content of extractive components for beer, and a relatively small variation in raw grains, six-rowed barley was not much favored among beer brewers due to its small grain size and a relatively large variation in grains, making two-rowed barley a more preferable choice for beer brewing. This is the reason why two-rowed barley has been named as malting barley. There is no such a plant called as "malting barley" (*biru-mugi*), and its botanical name is barley (*oomugi*). To be exact, malting barley is beer barley (*biru-oomugi*), or two-rowed barley for beer brewing, that is, a kind of name equivalent to noodle wheat and/or bread wheat. Ground (Milled) large-grain barley having less loss, that is, two-rowed barley, is used among various types of barley as a material for distilled spirit. Food barley includes such a kind of barley as well as other edible barley.

Two-rowed barley is characterized in its larger grain size in comparison with six-rowed barley, popularly used for barley tea and the like. The hull (so-called bran portion) of barley contains fat, proteins, and insoluble fibers, etc. Therefore, if the whole grain of barley (husked barley) is used for brewing, the quality of the resulting liquor will be poor. For this reason, approximately 35% of grain closer to its outer skin is removed for brewing purposes (this process is referred to as "65% polishing"). As explained above, since the skin portion of barley is removed for brewing, two-rowed barley, which has a relatively large grain size, is suitable. In a process of beer brewing, a malt-derived diastatic enzyme is used in order to saccharize starch contained in the material. In contrast, in a brewing process of distilled spirit, *Aspergillus oryzae* (*koji-kin*), which is a kind of fungus, is grown on the material; and subsequently, a diastatic enzyme produced by the *koji-kin* saccharizes the starch. This process is called as *koji* production (*seikou*). Two-rowed barley, which has a relatively large grain size, has another advantage in its easier manipulation in the process of *koji* production. As discussed above, two-rowed barley is the barley used for production of distilled spirit.

For the above reasons, it is respectfully submitted that Applicants' claims are clear and definite and it is requested that the rejection under 35 U.S.C. §112 be reconsidered and withdrawn.

II. The Rejection Under 35 U.S.C. §102 Based on Omori (JP2001-145472)

Claims 1-4 are rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Omori et al.

Applicants respectfully submit that the present invention is not anticipated by or obvious over the disclosures of Omori et al and request that the Examiner reconsider and withdraw this rejection in view of the following remarks.

The composition according to the present invention is produced by obtaining "an unadsorbed fraction obtained by subjecting a barley shochu stillage obtained as the by-product in the production of shochu from barley to solid/liquid separation and then subjecting the liquid fraction thus obtained to a separation treatment by adsorption." In contrast, the composition according to Omori is produced as follows; a liquid fraction is obtained by subjecting a barley shochu stillage (residual liquid), which is obtained as the by-product in the process of producing *shochu* (distilled spirit) from barley, to solid/liquid separation; and then, the liquid fraction thus obtained is subjected to alkali addition treatment to obtain an alkali soluble fraction; the alkali soluble fraction thus obtained is then neutralized with an acid to obtain a neutral soluble fraction; and finally, a precipitated fraction is obtained after addition of ethanol to the neutral soluble fraction."

As shown above, there are fundamental differences in production process between the composition according to the present invention and the resulting composition according to Omori (see also the drawings of Omori).

Another difference between the two compositions is percent composition. The composition according to the present invention contains the following elements (see, for example, Applicants' claim 4):

Organic Acid	2-8%
Polysaccharide	15-25%
Free Amino Acid	4-12%
Free Sugar	5-10%

The composition according to Omori contains the following elements:

Organic Acid	32-38%
Protein	28-34%
Hemicellulose	25-31%

Therefore, the compositions made by the processes of the cited art are completely different from the composition of the present invention. For example, there is no overlap in organic acid concentration.

Further, as set forth in further detail in Applicants' specification, one of ordinary skill in the art would not have expected the unexpected effects produced by a composition according to the present invention. That is, the inhibition of the onset of alcoholic liver injury is unexpected based on the known activity of inhibiting the onset of orotic acid-induced hepatopathy disclosed by Omori or based on the known activity of inhibiting the onset of D-galactosamine-induced hepatopathy disclosed by other publicly known documents.

Omori describes that a composition comprising an ethanol-insoluble fraction containing an organic acid, protein and hemicellulose and formed by subjecting a barley *shochu* stillage to solid-liquid separation to obtain a liquid fraction, adding an alkali to the liquid fraction to collect

an alkali-soluble fraction, neutralizing the alkali-soluble fraction with an acid to obtain a neutral soluble fraction and adding ethanol to the neutral soluble fraction has an activity of inhibiting the onset of orotic acid-induced hepatopathy in an experiment using rats.

Thus, Omori describes that the ethanol-insoluble fraction has an activity of inhibiting the onset of orotic acid-induced hepatopathy. However, it does not even suggest whether or not the ethanol-insoluble fraction has an activity of inhibiting the onset of alcoholic hepatopathy or an activity of healing it.

As stated above, an example of obtaining a fraction having an activity of inhibiting the onset of alcoholic hepatopathy and an activity of healing it from a barley *shochu* stillage has been to date entirely unknown.

The orotic acid-induced hepatopathy is known to be hepatopathy in which synthesis of fat in the liver is accelerated with orotic acid and migration of fat from the liver into blood is inhibited to thereby induce the fat liver. The D-galactosamine-induced hepatopathy is known to be hepatopathy in which necrosis of hepatocytes is accelerated with D-galactosamine to thereby induce hepatitis.

Meanwhile, the alcoholic hepatopathy includes, as noted earlier, alcoholic hepatitis, alcoholic fatty liver and alcoholic hyperlipemia induced by excess intake of alcohol, and it is objectively differentiated from the orotic acid-induced hepatopathy and the D-galactosamine-induced hepatopathy. That is, the alcoholic fat liver is known to be a fat liver in which neutral fat is accumulated in the liver by accelerating migration of a fatty acid from a fat tissue to the liver

with ethanol to accelerate synthesis of fatty acid or neutral fat in the liver, inhibiting decomposition of fatty acid in the liver and the like. The alcoholic hepatitis is known to be hepatitis which is induced such that acetaldehyde or acetic acid, a metabolite of ethanol or active oxygen generated in producing the same damages hepatocytes. The alcoholic hyperlipemia is known to be triggered such that excess neutral fat accumulated in the liver is released to blood in large quantities as a secretory very low density lipoprotein (VLDL). In such an alcoholic hepatopathy, it is known that lesion of hepatitis such as balloon-like swelling or necrosis of hepatocytes, or a fatty liver comprising hepatocytes containing large fatty drops is progressed mainly on the terminal hepatic vein peripheral region of the hepatic lobule. Incidentally, the liver is an assembly of a large number of the hepatic lobules each having a diameter of 1 mm in which the hepatic lobule partitioned by an interlobular connective tissue functions as one unit.

Accordingly, in view of the causative sequence of such hepatopathies, the alcoholic hepatopathy is objectively differentiated from the orotic acid-induced hepatopathy and the D-galactosamine-induced hepatopathy. Even though some ingredient is known to have an activity of inhibiting the onset of orotic acid-induced hepatopathy or D-galactosamine-induced hepatopathy or an activity of healing it, it can never be expected easily whether or not the very ingredient has also an activity of inhibiting the alcoholic hepatopathy or an activity of healing it.

Again, the effects achieved by the presently claimed composition are unexpected over the prior art.

For the above reasons, it is respectfully submitted that the subject matter of claims 1-4 is neither taught by nor made obvious from the disclosures of Omori et al and it is requested that the rejection under 35 U.S.C. §102 be reconsidered and withdrawn.

III. Pages 7-9 - The Rejection Under 35 U.S.C. §102 Based on Yamamoto

Claims 1-4 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Yamamoto (JP 2001-299268).

Applicants respectfully submit that the present invention is not anticipated by or obvious over the disclosures of Yamamoto and request that the Examiner reconsider and withdraw this rejection in view of the following remarks.

Yamamoto relates to a seasoning produced from sesame as protein material and barley as starch material by a soy-sauce fermentation method. It should be noted herein that the seasoning is produced through soy-sauce fermentation. After appropriate immersion in water, sesame subjected to steaming with a high-pressure vapor is mixed with pre-processed barley, where the barley was roasted with a roaster, etc. and then crushed/milled with a hammer mill crusher, etc. *Koji* is then grown therefrom. Then, a controlled brine solution is added thereto as mother water for *shikomi*. This process is followed by fermentation and aging. After fermentation and aging, a clear liquid portion is extracted by compression, followed by a process of firing (*hi-ire*) or filtration, and removing of lees (*oribiki*), etc.

Yamamoto does not disclose "distillation" or "a separation treatment by adsorption using a synthetic adsorbent" in the production process.

As described above, Yamamoto differs from the present invention in that Yamamoto uses sesame as material; Yamamoto employs a soy-sauce fermentation method in which a brine solution is added as mother water for *shikomi*, which distinguishes itself from brewing for production of distilled spirit; and Yamamoto uses a different type of *koji-kin* (soy sauce: *Aspergillus sojae*, distilled spirit: *Aspergillus kawacii*). In addition, Yamamoto further differs from the present invention in that Yamamoto does not include the process of subjecting the liquid fraction obtained after solid/liquid separation to a separation treatment by adsorption using a synthetic adsorbent. Thus, it is readily evident that the compositions obtained by the processes of Yamamoto are clearly different than the claimed compositions.

The description of Yamamoto is directed to a seasoning that contains a large amount of salt. On the other hand, the present invention relates to food having physiological functions. Another difference that makes the present invention further distinctive is the removal of component harmful to human body if taken excessively, where the removal is performed through a separation treatment by adsorption using a synthetic adsorbent, etc.

For the above reasons, it is respectfully submitted that the subject matter of claims 1-7 is neither taught by nor made obvious from the disclosures of Yamamoto and it is requested that the rejection under 35 U.S.C. §102 be reconsidered and withdrawn.

IV. The Rejection Under 35 U.S.C. §103

Claims 1-7 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Omori et al in view of Kaneuchi et al.

Applicants respectfully submit that the present invention is not anticipated by or obvious over the disclosures of Omori et al in view of Kaneuchi et al and request that the Examiner reconsider and withdraw this rejection in view of the following remarks.

The teachings of Omori are discussed above. The disclosures of Kaneuchi et al do not overcome the deficiencies in Omori discussed above. Kaneuchi teaches a fraction derived from beer lees, where the wet beer lees is compressed into flakes and milled, followed by sieving treatment in the presence of water. The production process disclosed by Kaneuchi does not include "*koji*-production", "distillation", or "a separation treatment by adsorption using a synthetic adsorbent".

As already mentioned, *koji*-production is a biological manipulation in which a diastatic enzyme produced by *koji-kin* saccharizes the starch. Since *koji-kin* produces not only amylase but also a wide variety of protease and peptidase, protein is subjected to various modifications (e.g. deoligomerization) during the process of *koji*-production. In the distillation process, heating treatment causes various reactions such as association and dissociation of protein. Therefore, the degrees of polymerization and coupling of beer lees, not subjected to a *koji*-production process and a distillation process, differ from those of the residual liquid of distilled spirit, subjected to these processes, even if they contain similar amino acids that constitutes the protein and peptides.

This means that these compositions are different and have disparate characteristics that are completely different from each other.

See also Table 7 and Table 8 of the present application. There is some overlap between the glutamic acid content of the present invention and that described by Kaneuchi (JP8-157385). However, the content of amino acid such as glycine and serine disclosed by Kaneuchi does not fall within the range of the embodiments of the subject application.

Content described in Kaneuchi: 3.66 percent by weight of glycine, 4.49 percent by weight of serine.

Content described in the subject application: 4 to 20 percent by weight of glycine, 4 to 8 percent by weight of serine.

The above difference additionally shows that these compositions are completely different from each other.

As described in paragraphs [0017] and [0018] of Kaneuchi, the fraction is further concentrated using a protein-extracting reagent, and the resulting concentrate is subjected to usual dialysis and ultra-filtration, followed by freeze-drying to obtain a protein fraction. The resulting protein fraction is obtained as freeze-dried powder, not the freeze-dried powder of unadsorbed fraction that is discussed therein.

> [0017] Furthermore, according to the present invention, protein having 10-40 percent of glutamine and glutamic acid with respect to the percent of constituent amino acid may be separated from the above fraction derived from

beer lees. The amino acid composition of the protein obtained in that manner was almost the same as the amino acid composition of the fraction derived from beer. For example, the above fraction derived from beer lees/husk is heated to reflux for a few hours with the extracting reagent described in the next paragraph. Subsequently, the mixture is filtered to obtain a solution having a high protein concentration. This solution is subsequently subjected to dialysis, and ultra-filtration, etc., in an ordinary manner. Finally, a protein fraction is obtained by a freeze-drying method, etc. The protein fraction may be purified by an ammonium sulfate precipitation method.

[0018] The composition of the protein extraction reagent:

Thirty gram of sodium lauryl sulfate, 18.6 g of EDTA disodium salt, 6.18 g of $Na_2B_4O_7$, 4.56 g of $NaHPO_4$, and 10 ml of ethylene glycol monoethyl ether were determined using 1 L of distilled water to adjust the pH of the solution to 6.9 to 7.1. For use, one hundred milliliter of the resulting solution is added per one gram of a sample. The aforementioned unadsorbed fragment has the form of freeze-dried powder, ... (text omitted).

For the above reasons, each of the cited references is quite different from Applicants' claimed invention. Moreover, even if the cited references are combined, it is respectfully submitted that it would not have been obvious to one of ordinary skill in the art to select the

inventive composition and it is respectfully submitted that the beneficial results achieved by the inventive composition would not have been expected to one skilled in the art.

For the above reasons, it is respectfully submitted that the subject matter of claims 1-7 is neither taught by nor made obvious from the disclosures of Omori et al in view of Kaneuchi et al, either alone or in combination, and it is requested that the rejection under 35 U.S.C. §103(a) be reconsidered and withdrawn.

V. Conclusion

In view of the above, Applicants respectfully submit that their claimed invention is allowable and ask that the rejection under 35 U.S.C. §112 and the rejections under 35 U.S.C. §§102 and 103 be reconsidered and withdrawn. Applicants respectfully submit that this case is in condition for allowance and allowance is respectfully solicited.

If any points remain at issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the local exchange number listed below.

If this paper is not timely filed, Applicants respectfully petition for an appropriate extension of time. The fees for such an extension or any other fees that may be due with respect to this paper may be charged to Deposit Account No. 50-2866.

Respectfully submitted,

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Sworn English language translation of JP 2002-250992;
Silvestre et al, Agric. Food Chem., 42, 2778-82 (1994)